# THE ACTION OF CERTAIN ACID REAGENTS ON THE SUBSTITUTED UREAS.

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1915.

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by

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A thesis submitted to the Department of Chemistry and the faculty of the Graduate School in partial fulfillment of the requirements for the Master's degree.

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Dept. of Chem.

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This investigation has been undertaken with the purpose of studying the action of certain acid reagents on the substituted ureas and isourea ethers. The main question which arises in a study of these compounds is the reaction of the anilido hydrogen toward, and its replacement by, such reagents. The quantity of work which has been done along this line is rather limited although this field for research is quite extensive.

During the last few years Dr. F. B. Dains has carried on a series of investigations on this class of and in a paper, published in the Journal of the American Chemical Society, April, 1900, he has shown that when thio carbanilide and organic acids were heated together at a temperature of 140°C. to 160°C., hydrogen sulphide and carbon dioxide are evolved and diphenyl urea and an anilide may be separated from the residue.

The main reaction is:

$$\begin{matrix} R\text{-}N\text{-}H \\ \quad\diagdown \\ \quad\quad C{=}S \\ \quad\diagup \\ R\text{-}N\text{-}H \end{matrix} + RCOOH \longrightarrow RNCS + RNH_2 \cdot RCOOH$$

At the temperature of the reaction the amine and acid unite.

$$RCOOH + RNH_2 \longrightarrow RNHCOR + H_2O$$

At the same time the mustard oil is attacked

$$RNCS + RCOOH \longrightarrow RNHCOR + COS \quad (H_2S \quad CO_2 \quad COS \quad H_2O)$$

The products usually obtained in the reaction are

carbon dioxide, hydrogen sulphide, water, the anilide, mustard oil and carbanilide. The preceeding equations account for all of these products except the carbanilide. Dr. Dains gives the following theory for its formation as being quite probable: at the high temperatures employed, the thio carbanilide is more or less dissociated into carbodiimide and hydrogen sulphide.

The carbodiimide then reacts with the organic acid as follows:

$$(RN)_2C + 2RCOOH \longrightarrow (RNH)_2CO + (RCO)_2O$$

Dibasic asids, when heated with thio carbanilide were found to form an anilide, carbon dioxide and hydrogen sulphide.

$$\begin{matrix} R\text{-}N\text{-}H \\ \quad\diagdown\!\!\diagup C{=}S \\ R\text{-}N\text{-}H \end{matrix} + \begin{matrix} H\text{-}O\text{-}C{=}O \\ \quad\quad | \\ H\text{-}O\text{-}C{=}O \end{matrix} \longrightarrow CO_2 + H_2S + \begin{matrix} CONHR \\ | \\ CONHR \end{matrix}$$

The general reaction between an acyl chloride and a dialphyl thio urea was found to be

$$\begin{matrix} R\text{-}N\text{-}H \\ \quad\diagdown\!\!\diagup C{=}S \\ R\text{-}N\text{-}H \end{matrix} + RCOCl \longrightarrow \begin{matrix} R\text{-}N\text{-}H \\ \quad\diagdown\!\!\diagup C{=}S \\ R\text{-}N{=}C\text{-}O\text{-}R \end{matrix} + HCl$$

$$\begin{matrix} R\text{-}N\text{-}H \\ \quad\diagdown\!\!\diagup C{=}S \\ R\text{-}N{=}C\text{-}O\text{-}R \end{matrix} + HCl \longrightarrow RNCS + RNHCOR + HCl$$

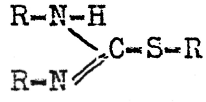
Mustard oil and an acyl anilide were the main products while occasionally small quantities of amidine bases were formed.

In the case of the isourea ethers it is a simple matter to prepare the acyl derivative but with the thio

ureas similar compounds are obtained only under very favorable conditions. These products have been obtained, however, by McCreath (Ber. 8, 1181) by the addition od anilides to isocyanates. For instance, the acyl derivative of diphenyl urea is produced by the action of phenyl isocyanate and acetanilide.

The acyl ureas and the acyl derivatives of the isourea ethers are not extremely stable and, when heated above their melting points, decompose into anilides and cyanates or anilides and mustard oils.

The experimental work described in this paper has been limited to three general types of reactions: (1) the products formed by treatment of the substituted thioureas with urea chlorides; (2) the interaction of acid reagents with the isourea ethers of the general formula



and (3) the transformation of the allyl thio ureas into the thiazole bases.

The substituted ureas have been prepared by the addition of anilines to the various mustard oils, a method which was described by Gerhardt (Ber. 17, 2090).

The isourea ethers were obtained by boiling an alcoholic solution of thio carbanilide with an alkyl iodide, on a water bath with a reflux condenser for several hours.

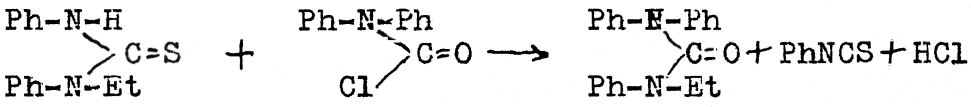
# EXPERIMENTAL.

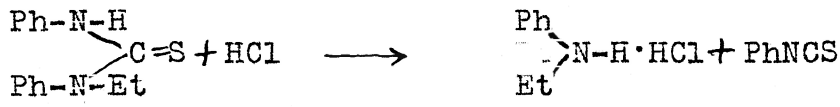
## DI-PHENYL ETHYL THIO UREA and DI-PHENYL UREA CHLORIDE.

Di-phenyl ethyl thio urea was prepared by treating ethyl aniline with phenyl mustard oil. The two substances were dissolved in a little alcohol and allowed to stand over night. A considerable quantity of heat is evolved and the di-phenyl ethyl thio urea solidifies in a hard cake. It was washed with water and dilute hydrochloric acid and was then recrystallized from gasoline.

Ten grams of this urea was mixed with an equivalent amount of di-phenyl urea chloride and heated in a large test tube in an oil bath at 150°C. to 160°C. for two hours, The reaction product was a dark green resinous mass, which was transferred to a small flask and subjected to steam distillation. Phenyl mustard oil distilled over.

On filtering off the liquid in the distilling flask and adding sodium hydroxide solution, ethyl aniline was precipitated. The presence of ethyl aniline hydrochloride in the solution is due to the decomposition of the ethyl di-phenyl thio urea by the hydrogen chloride which is formed by the main reaction.





The green mass in the flask was extracted with boiling gasoline. On allowing the gasoline extract to stand a white solid crystallized out. This product is readily soluble in alcohol and moderately so in ether, glacial acetic acid and gasoline. It was recrystallized from the latter solvent, giving pure crystals, mp. 79°C.

This compound is evidently the tri-phenyl ethyl urea prepared by Michler (Ber. 14, 2185) by the action of ethyl aniline with di-phenyl urea chloride, since the two substances melt at the same temperature.

DI-PHENYL ETHYL THIO UREA and METHYL PHENYL UREA CHLORIDE.

This reaction is very similar to the one preceding. Equal mols of the urea and urea chloride were mixed and heated in an oil bath at 150°C. to 160°C. for two hours. The reaction product, a resinous mass, on being steam distilled gave phenyl mustard oil.

The liquid in the flask was poured off, and gave a precipitate of ethyl aniline on being made alkaline with sodium hydroxide. The presence of ethyl aniline hydrochloride, as stated above, is due to the decomposition of the di-phenyl ethyl thio urea.

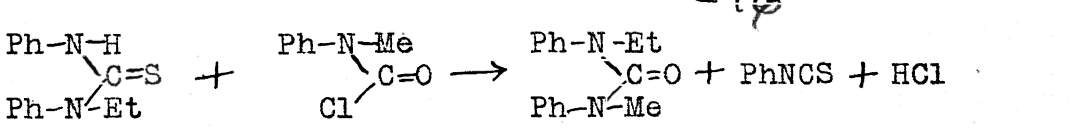
The gummy residue in the flask was extracted with

boiling gasoline and the solution allowed to stand. A white solid crystallized out and recrystallized from the the same solvent. This urea, mp. 74°C., is readily soluble in alcohol and benzene but only sparingly so in ether.

Analysis of the compound as di-phenyl ethyl methyl urea requires 11.02% of nitrogen. By the "absolute nitrogen" method 0.2075 grams of the sample gave 21.42 cc of moist nitrogen at 25°C. and 740 mm of mercury. With a second determination 0.2080 grams of sample gave 21.65 cc of moist nitrogen at 23°C. and 739 mm of mercury.

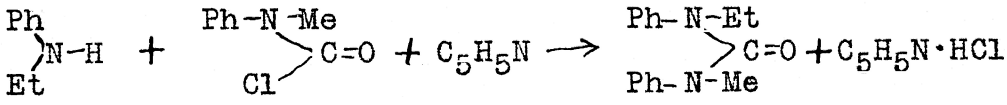
| Found | Theory |
|---|---|
| 11.15 | 11.02 |
| 11.35 | |

$C_{16}H_{18}ON_2$



ETHYL ANILINE and METHYL PHENYL UREA CHLORIDE

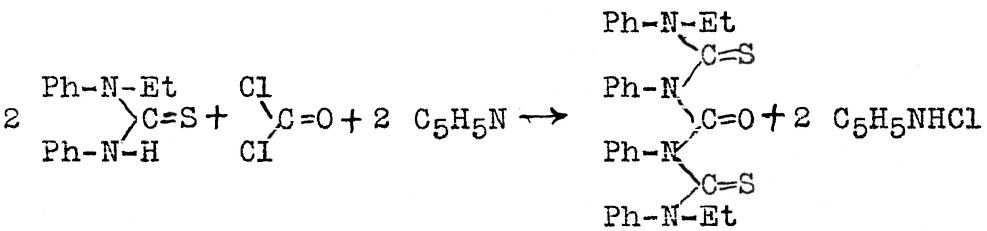
with PYRIDINE.



Molecular quantities of the original materials were heated in an oil bath for a short time (30 min.) at 140°C. The pyridine hydrochloride was washed out with water and the residue was dissolved in hot gasoline and allowed to stand. The urea crystallized out and was purified from the same solvent. It is also soluble in alcohol, and benzene

but insoluble in water. This urea melts at 73°C. to 74°C. and is the aame product that was prepared in the preceding experiment. On mixing the two compounds no depression of the melting point could be detected.

DI-PHENYL ETHYL THIO UREA and PHOSGENE with PYRIDINE.



The substances were used in the ratio expressed by the equation, and dissolved in benzene separately. The solutions of urea and pyridine were placed in a side-necked flask, to which was connected a reflux condenser and a dropping funnel. The phosgene, dissolved in benzene, was placed in the dropping funnel and slowly added to the urea and the pyridine. Since considerable heat is evolved it was thought well to cool the flask in cold water.

The reaction is rather vigorous and pyridine hydrochloride is soon precipitated. After all of the phosgene was added the reaction was allowed to go on undisturbed for nearly an hour. The benzene solution was filtered off and concentrated. A crystalline product was obtained which was purified from alcohol, mp.166$_0$C. It was considered to

be carbonyl di(di-phenyl ethyl thio urea) as indicated in the equation.

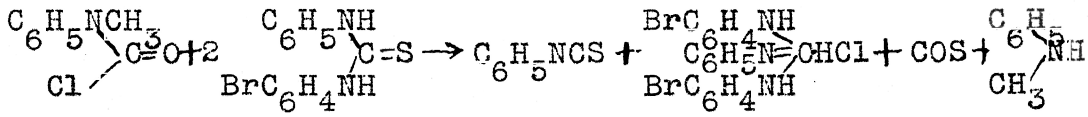
On analysis 0.2304 grams of the substance gave 22.84cc. of moist nitrogen at 26°C. and 738 mm.of mercury. Also 0.2510 grams of the sample gave 24.52 cc. of moist nitrogen at 25°C. and 737 mm. of mercury.

| Found | Theory |
|---|---|
| 10.62 | 10.41 |
| 10.50 | |

The sulphur atoms are not replaced by oxygen when a solution of the substance is boiled with mercuric oxide.

## PARA MONO BROM DI-PHENYL THIO UREA and METHYL PHENYL UREA CHLORIDE.

One mol of methyl phenyl urea chloride was mixed with two mols of p-mono-brom di-phenyl thio urea, and the mixture heated in an oil bath at 140°C. to 150°C. for an hour. A gas was given off which darkened lead acetate paper. The reaction product, a green resinous mass, on distillation with steam, gave phenyl mustard oil and a trace of methyl aniline. The gummy product remaining in the flask was extracted with hot benzene. On cooling this solution a white solid separated out and, when purified from benzene, meltdd at 240°C. to 243°C. It was a hydrochloride of di-brom triphenyl guanidine.



The compound was analysed by decomposing a known weight of it in liquid ammonia with metallic sodium. After the ammonia had evaporated off the sodium salts were dissolved and titrated with a standard solution of silver nitrate. One third of the number of cubic centimeters of solution used were taken to calculate the chlorine and the remainder used for the estimation of bromine.

Analysis as $C_{19}H_{16}N_3ClBr_2$

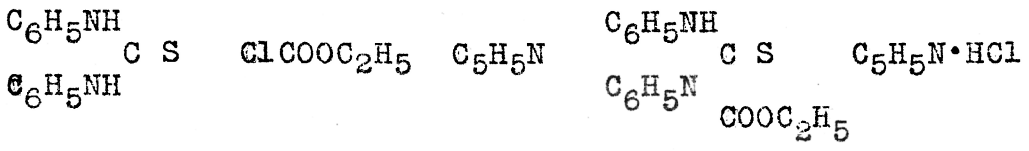
| | Found | Theory |
|---|---|---|
| Cl | 6.66 | 6.70 |
| | 6.50 | |
| Br | 30.0 | 30.2 |
| | 29.3 | |

The addition of alkali, either sodium carbonate or ammonium hydroxide, to the hydro-chloride of the base, gave a product which was gummy both when dried on the plate or in a dessicator, making the effort to obtain the pure, free base unsuccessful.

## DI-PHENYL THIO UREA AND CHLOR FORMIC ETHYL ESTER withPYRIDINE.

Equal mols of the substances were dissolved in benzene and boiled on a water bath with a reflux condenser for

thirty minutes.



Pyridine hydrochloride was precipitated and the benzene solution was poured off and washed with water and dilute hydrochloric acid. On standing a yellow solid crystallized from the benzene solution and was purified from alcohol. This product is also readily soluble in chloroform and gasoline but only moderately so in ether. It melts at 95°C. and is described by Seidel (Jour. pr. Chem. 32, 261-277).

On analysis 0.2387 grams of the substance gave 20.87 cc of moist nitrogen at 29°C. and 738 mm. of mercury. Also 0.2560 grams of the sample gave 22.74 cc. at 26°C. and 737 mm. of mercury.

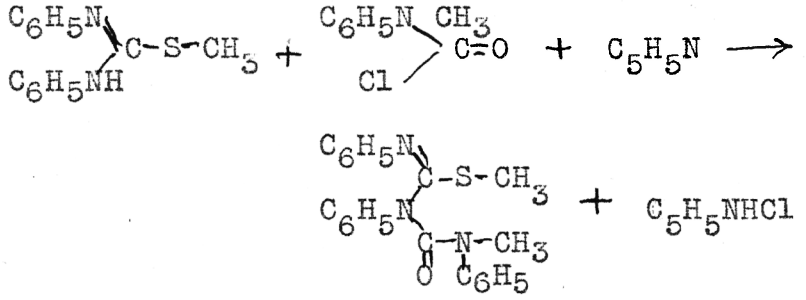
Analysis as $C_{16}H_{16}O_2N_2S$

| Found | Theory |
|---|---|
| 9.21 | 9.33 |
| 9.50 | |

THE METHYL ETHER of DI-PHENYL THIO UREA and METHYL PHENYL UREA CHLORIDE with PYRIDINE.

From theserreagents we would expect to obtain a derivative of the urea ether in which a Ph Me NCO group would

would replace the anilido hydrogen of the urea ether according to the following equation:



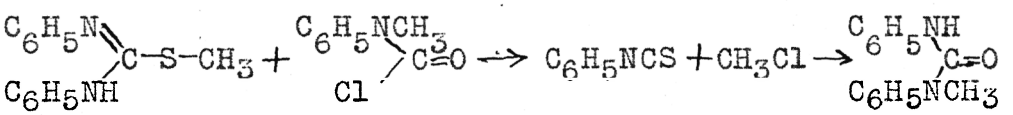
When molecular quantities of each compound were mixed in a lagge test tube and heated on an oil bath at 160°C. for an hour and the reaction product, a green oily mass, dissolved in alcohol and diluted with water, phenyl mustard oil was precipitated in good quantity. The supernatant liquid was poured off and on being allowed to stand for a short time a white solid crystallized out. It was purified from gasoline, giving colorless crystals which melted at 105°C. and on analysis for nitrogen gave 12.7 per cent of that element. The formulas supposed in the equation requires 11.2 per cent nitrogen. The other possibility is that there is a loss of mustard oil and that methyl di-phenyl urea was produced which is in accord with the analysis and the observation of the separation of the phenyl mustard oil.

As a standard of comparison methyl di-phenyl ~~thio~~ urea was prepared from aniline and methyl phenyl urea chloride. It was obtained in a pure state by recrystallization from gasoline and melted at 104°C. which was the melting point

of the compound formed by the above reaction.

These facts show that the reaction, supposed to take place, as set forth in the preceding equation, in reality proceeds along a different line and indicates that the pyridine has no part in the process.

The experiment was repeated by heating the original materials in a sealed glass tube at 150°C. for two hours. No pyridine was used.



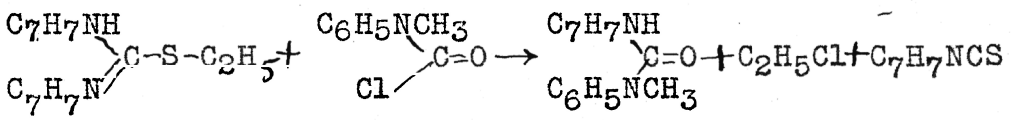
The tube opened with pressure giving the odor of mercaptan and an inflamable gas. The pressure extinguished the flame making it uncertain what gas was produced. A repitition of the experiment gave a gas which burned with a blue flame which is the nature of methyl chloride. Phenyl mustard oil was easily obtained from the reaction product by diluting the alcoholic solution with water. Extracting the products of the reaction with gasoline gave, on standing, a nearly pure yield of methyl di-phenyl urea, mp. 106°C., which was recrystallized from gasoline. This urea is quite soluble in the ordinary organic solvents. On analysis 0.2750 grams of the sample gave 31.70 cc. of moist nitrogen at 24°C. and 740 mm. of mercury.

| Found | Theory |
|---|---|
| 12.63 | 12.41 |

All efforts to bring about this reaction by boiling the components in benzene solution met with no success.

## THE ETHYL ETHER of ORTHO DI-TOLYL THIO UREA and METHYL PHENYL UREA CHLORIDE.

Molecular quantities of the two substances were heated in a sealed tube at 150°C. for two hours. The tube opened with pressure giving ethyl chloride which burned with a greenish flame. Ortho tolyl mustard oil was easily obtained by diluting the alcoholic solution of the reaction product with water. A gasoline extract of the reaction product gave o-tolyl methyl phenyl urea which was purified from alcohol, mp. 117°C.



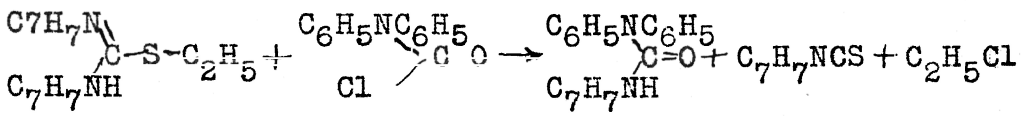
This urea was further identified by comparison with the product formed from ortho toluidine and methyl phenyl urea chloride when heated at a temperature of 125°C. This compound melted at the same point as the one formed in the main reaction. On mixing the two bodies no depression of the melting point could be detected.

On analysis 0.2080 grams of the sample gave 22.51 cc. of moist nitrogen at 25°C. and 740 mm. of mercury. Also 0.2195 grams of the substance gave 22.85 cc. of moist nitrogen at 29°C. and 738 mm. of mercury.

Analysis as $C_{15}H_{16}ON_2$

| Found | Theory |
|---|---|
| 11.72 | 11.66 |
| 11.50 | |

THE ETHYL ETHER of ORTHO DI-TOLYL THIO UREA and DI-PHENYL UREA CHLORIDE.



The reacting materials were mixed together, mol for mol, and heated under the same conditions which prevailed in the preceding experiment. The tube opened with pressure; ethyl chloride escaped and burned with a green flame. The reaction product, a thick oily mixture, was removed to a flask and distilled with steam. Ortho tolyl mustard oil distilled over and was extracted with ether. The solid material remaining in the flask was dissolved in gasoline. On allowing this solution to stand crystals of o-tolyl di-phenyl urea were formed. This urea is readily soluble in alcohol, benzene and chloroform and moderately so in gasoline, from which it was recrystalized, mp. 85°C.

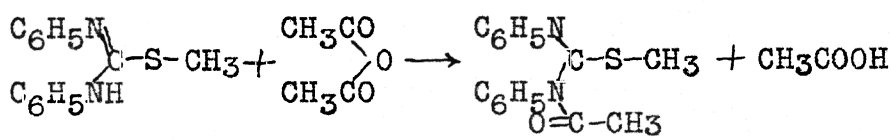
On analysis 0.2693 grams of the sample gave 22.39 cc of moist nitrogen at 23°C. and 738 mm of mercury. Also 0.2215 grams of the substance gave 19.00 cc of moist nitrogen at 740 mm of mercury.

Analysis as $C_{20}H_{18}ON_2$

| Found | Theory |
|---|---|
| 9.05 | 9.27 |
| 9.11 | |

THE METHYL ETHER OF DI-PHENYL THIO UREA and ACETIC ANHYDRIDE.

One mol of the urea was heated at 115°C. for fifteen minutes with rather more than an equivalent amount of acetic anhydride. The reaction product was a light yellow liquid and was dissolved in alcohol. On diluting this solution with water and allowing it to stand over night a white solid was obtained which was purified from hot dilute alcohol. The pure product melts at 70°C.



On analysis 0.2250 grams of the sample gave 20.84 cc of moist nitrogen at 24°C. and 739 mm of mercury. Also 0.2775 grams of the substance gave 25.60 gc of moist nitrogen at 26°C. and 740 mm of mercury.

Calculated as $C_{16}H_{16}ON_2S$

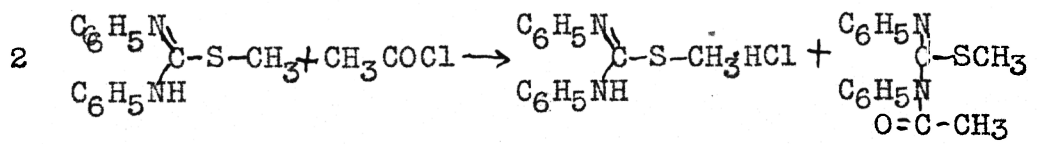
| Found | Theory |
|---|---|
| 10.04 | 9.78 |
| 9.90 | |

The addition of the $CH_3CO$ group had greatly reduced the basic properties of this isourea ether. The acetyl derivative is only faintly soluble in dilute acids and does not form a solid hydrochloride by passing dry hydrogen chloride into its benzene solution. Neither does it form a picrate when a benzene solution of picric acid is added to a benzene solution of the substance. Boiling alkalis split off the acetyl group giving the original product.

THE METHYL ETHER of DI-PHENYL THIO UREA and ACETYL CHLORIDE.

Two mols of the isourea ether were dissolved in benzene and to this solution was added one mol of acetyl chloride slowly. On allowing the contents of the flask to stand over night a resinous product was precipitated. The supernatant liquid was poured off and, when concentrated, gave cubical crystals which were purified from gasoline. This is the same product as that obtained in the preceding reaction. It melts at 70°C.

The gummy precipitate which was formed in the flask was dissolved in alcohol and treated with dilute alkali. A white precipitate was thrown down which melted at 106°C. and was the original material.



This acetyl derivative is readily soluble in alcohol, chloroform, gasoline and benzene but only moderately so in ether.

## THE ETHYL ETHER of ORTHO DI-TOLYL THIO UREA and META NITRO BENZOYL CHLORIDE with PYRIDINE.

Molecular quantities of the reacting substances were used. The urea ether and pyridine were placed in a flask and dissolved in benzene. The nitro benzoyl chloride was slowly added to this solution. A small amount of heat was evolved and a solid precipitated, which was shown to be pyridine hydrochloride by treating it with aqueous sodium hydroxide.

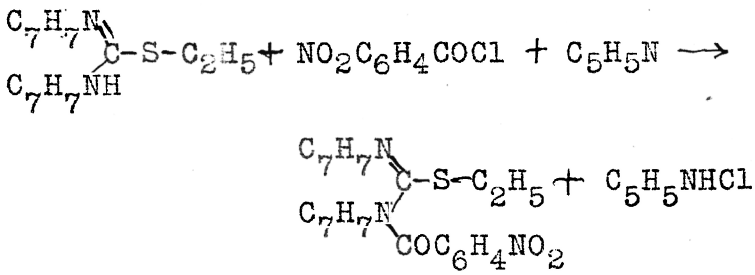
Slow evaporation of the benzene solution gave a product, which, when recrystalized from benzene, melted at 122°C.

0 On analysis 0.3015 grams of the sample gave 27.4 cc of moist nitrogen at 24°C. and 739 mm of mercury. On a second determination 0.2775 grams of the substance gave 25.6 cc of moist nitrogen at 26°C. and 740 mm of mercury.

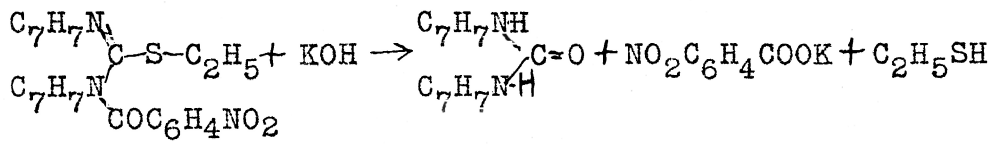
Calculation as $C_{24}H_{23}O_3N_3S$

| Found | Theory |
|---|---|
| 9.85 | 9.70 |
| 9.90 | |

This compound is a meta nitro benzoyl derivatative of the original isourea ether.



For further identification of this derivative of the isourea ether, the substance was boiled in alcoholic potash for about thirty minutes.



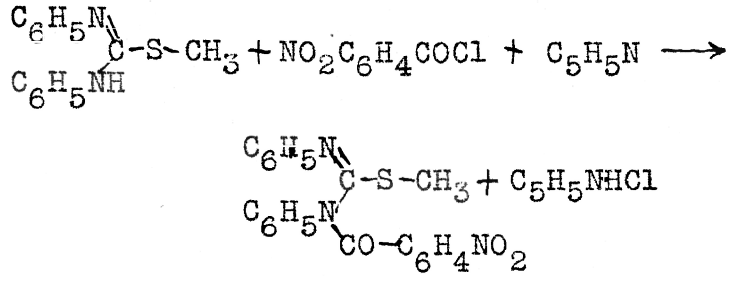
The odor of ethyl mercaptan soon became quite noticeable. On cooling the solution and diluting with water the ortho di-tolyl urea separated out and was identified by its melting point, 250°C. The supernatant solution was poured off and concentrated on the hot plate. On making the solution acidic with hydrochloric acid meta nitro benzoic acid was precipitated and identified by its melting point, 141°C.

## THE METHYL ETHER of DI-PHENYL THIO UREA and META NITRO BENZOYL CHLORIDE With PYRIDINE.

This reaction is very similar to the one preceding and was carried out under the same general conditions.

Molecular quantities of the isourea ether and pyridine were dissolved in benzene and to this solution the meta nitro benzoyl chloride in a little benzene, was slowly

added with constant shaking.



On allowing the flask to stand over night pyridine hydrochloride was precipitated. The benzene solution was poured off and washed with water and dilute hydrochloric acid to remove any excess pyridine. The benzene solution was concentrated somewhat and on standing, a resinous material settled out, which was purified from gasoline. It melts at 101°C. and is the meta nitro benzoyl derivative of the original isourea ether as illustrated in the equation, This product is also soluble in chloroform and alcohol but recrystalization from these solvents did nor yield a good pure sample. The basic properties of the original substance have been almost entirely over come by the addition of the nitro benzoyl radical.

On analysis 9.2510 grams of the sample gave 19.25 cc of moist nitrogen at 23°C. abd 738 mm of mercury. Also 0.2257 grams of the substance gave 22.54 cc of moist nitrogen at 28°C. and 740 mm of mercury.

Calculation as $C_{21}H_{17}O_3N_3S$

| Found | Theory |
|---|---|
| 10.51 | 10.70 |
| 10.60 | |

ALLYL PHENYL THIO UREA and BENZOYL CHLORIDE

with PYRIDINE.

Molecular quantities of these reagents were dissolved in benzene separately and the benzoyl chloride was slowly added to the solution of urea and pyridine. On allowing the flask to stand over night a white precipitate was formed which proved to be pyridine hydrochloride. The benzene solution was poured off and washed with water and dilute hydrochloric acid to remove any excess pyridine. When the solution was allowed to evaporate at room temperature it gave a pure crystalline product which melted at 125°C. and was considered to be the benzoyl derivative of allyl phenyl thio urea.

$$\begin{matrix} C_3H_5NH \\ C_6H_5NH \end{matrix}\!\!>\!C\!=\!S + C_6H_5COCl + C_5H_5N \rightarrow \begin{matrix} C_3H_5NH \\ C_6H_5N\!-\!COC_6H_5 \end{matrix}\!\!>\!C\!=\!S + C_5H_5NHCl$$

On analysis 0.2685 grams of the sample gave 23.8 cc of moist nitrogen at 24°C. and 739 mm of mercury.

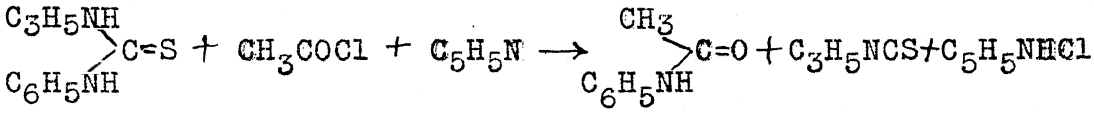
Calculation as $C_{17}H_{16}ON_2S$

| Found | Theory |
|---|---|
| 9.61 | 9.46 |

When the benzene solution was concentrated on the hot plate the crystalline product which was obtained was shown to be benzanilide, mp. 160°C. This would indicate that at boiling temperatures the benzoyl deritative of the original thio urea is decomposed into the anilide and allyl mustard oil.

The contents of the flask were distilled with steam to remove any allyl mustard oil and the distillate was made stongly alkaline with concentrated ammonia. On standing, allyl thio urea was obtained which was identified by its melting point.

ALLYL PHENYL THIO UREA and ACETYL CHLORIDE with PYRIDINE.

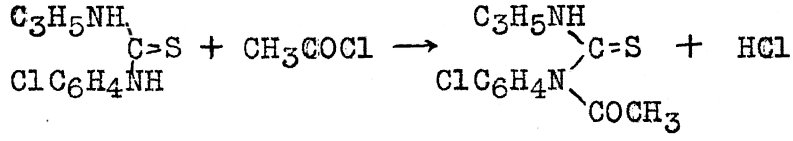


The reacting materials were taken in the proportion indicated by the equation and dissolved in benzene separately. The acid chloride was added to the solution of the urea and pyridine and the flask allowed to stand for an hour. Quite an appreciable quantity of heat was evolved and a white precipitate separated out which was pyridine hydrochloride. The supernatant benzene solution was decanted into a separatory funnel and washed with water until free from pyridine. On allowing the solution to evaporate at room temperature, a nearly pure solid crystallized out and was shown to be acetanilide, mp. 112°C. When the liquid remaining in the flask was subjected to steam distillation, allyl mustard oil was carried over. It was extracted from the distillate with benzene and a little aniline was added. After the mixture had stood for two or three days allyl phenyl thio urea crystallized out.

The acetyl derivative of allyl phenyl thio urea is evidently easily decomposed so that it is not obtained even the solution was allowed to crystallizw at room temperature.

ALLYL PARA CHLORPHENYL THIO UREA and ACETYL CHLORIDE.

Ten grams of the urea was dissolved in benzene and an equivalent amount of acetyl chloride was added with constant shaking. A small amount of heat was evolved and the flask was allowed to stand for an hour. A solid separated out which was insoluble in water and dilute acids. Concentration of the benzene solution gave more of the same compound. It was purified from alcohol, mp. 84°C. and proved to be an acetyl derivative of the original urea.



Analysis of the compound as $C_{12}H_{13}N_2SClO$

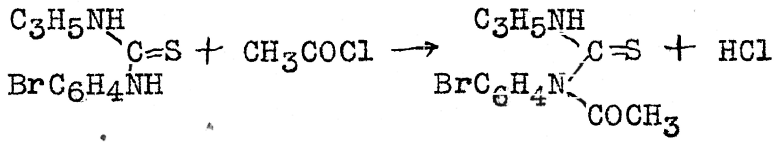
| Found | Theory |
|---|---|
| 13.50 | 1321 % chlorine |

There is a possibility that the acetyl group is attached to the other nitrogen atom near the allyl group. When the product was heated to a few degrees above its melting point for a few minutes, it decomposed into allyl mustard oil, which was recognized by its strong odor, and, on extracting the contents of the tube with hot water, a compound was obtained which, although not pure, gave a

good copper wire test for halogen and was thought to be p-chlor acetanilide. It was not sufficiently pure to be identified by a melting point.

ALLYL PARA BROMPHENYL THIO UREA and ACETYL CHLORIDE.

Equivalent quantities of these reagents in benzene solution react with the evolution of heat giving a crystalline product, on standing, which, when purified from alcohol, melted at 86°C. This product was not soluble in acids and when boiled in alcoholic potash the acetyl group was hydrolyzed off, giving the original urea. When the acetyl derivative was heated above its melting point for a short time, allyl mustard oil and p-bromacetanilide were obtained. These observations indicate that the reaction proceeds as follows:



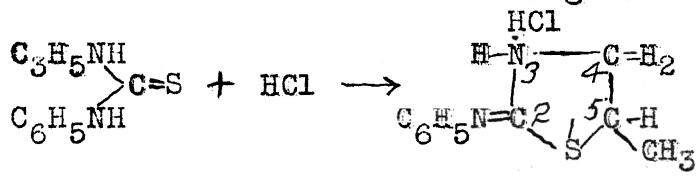
Analysis as $C_{12}H_{13}N_2OSBr$ by liquid ammonia method

| Found | Theory |
|---|---|
| 24. 11 | 24.44 % bromine |

In all of the preceeding experiments acyl derivatives have been obtained by the reaction of the acid chlorides with the substituted ureas or isourea ethers, or such compounds, if formed, were decomposed during the reaction into mustard oils and anilides. The allyl thio ureas under some conditions have a tendency toward rearrangement, thus

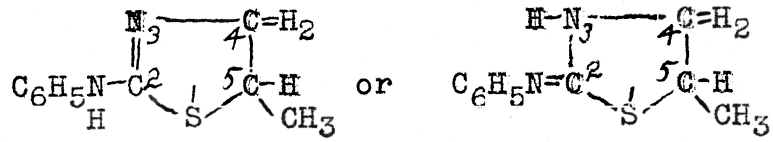
forming the thiazole bases.

Young and Crookes (Jour. Chem. Soc. 89, 59-76) have shown that allyl phenyl thio urea, when heated in a closed vessel with concentrated hydrochloric acid at 100°C., is converted into a thiazole according to the following equation.



Whether the hydrogen atom is attached to the nitrogen atom of the ring or the nitrogen atom outside of the ring is still somewhat of an open question.

When 2-phenyl imido, 4-methyl thiazole was treated with methyl iodide, the compound, which was obtained, contained a methyl group in position 3, instead of being connected to the nitrogen of the anilido group. This and similar experiments led Young and Crookes to adopt the above formula in preference to the configuration where the hydrogen atom is attached to the nitrogen outside of the ring.

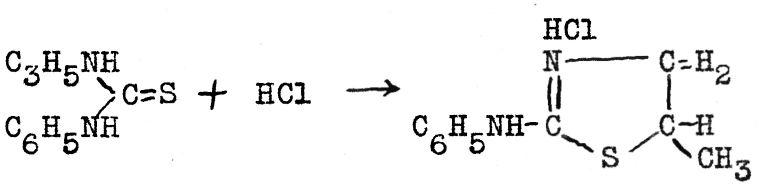


In a later work the writer hopes to study this class of compounds more extensively. If this thiazole contains a replaceable hydrogen at position 3, it would be interesting to synthesize such a compound from allyl aniline and phenyl mustard oil, and converting the allyl di-phenyl thio urea thus obtained into the thiazole, which must then

contain a phenyl group attached to each nitrogen atom.

ALLYL PHENYL THIO UREA and CONCENTRATED HYDROCHLORIC ACID.

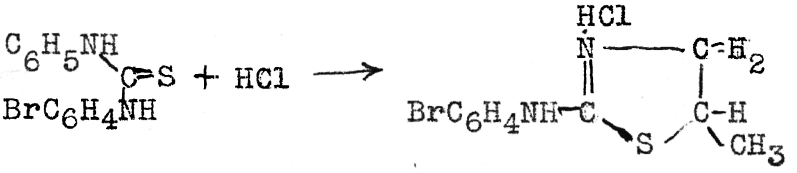
Fifteen grams of allyl phenyl thio urea and nearly three times that weight of pure, concentrated hydrochloric acid were placed in a pressure flask and immersed in a water bath. The water was heated to boiling and maintained at that temperature until all of the urea had dissolved. This required nearly an hour. The liquid was then poured into a beaker, diluted with water, and made alkaline with strong sodium hydroxide solution. A white basic solid was precipitated and purified from alcohol, mp. 116°C. Its picrate melts at 155°C. This thiazole has been formerly prepared by Young and Crookes ( Jour. Chem. Soc. 89, 66).



ALLYL PARA BROMPHENYL THIO UREA and CONCENTRATED HYDROCHLORIC ACID.

Ten grams of this urea was placed in a pressure flask and treated as in the above experiment. When the urea had entirely dissolved the liquid was poured out into a beaker, diluted with water and made alkaline with a concentrated s solution of sodium hydroxide. The white solid which was purified from hot dilute alcohol, giving pure crystals

which melt at 107°C.



Analysis of this 2-p-brom phenyl amido, 5-methyl, 4,5-dihydro thiazole as $C_{10}H_{11}N_2SBr$

0.2685 grams of the sample gave 26.80 cc of moist nitrogen at 26°C. and 738 mm of mercury.

0. 2930 grams of the substance gave 29.50 cc of moist nitrogen at 29°C. and 740 mm pressure.

| Found | Theory |
|---|---|
| 10.70 | 10.40 |
| 10.63 | |

ALLYL PARA BROMPHENYL THIO UREA and ACETYL CHLORIDE.

Equivalent quantities of these reagents were heated on a water bath for twenty minutes . The oily product was dissolved in alcohol and made alkaline with sodium carbonate solution. A precipitate was formed which, when purified from alcohol, melted at 107°C. This is the same product as that prepared in the preceeding experiment. It is soluble in the ordinary organic solvents and dilute acids. It gave a picrate which melted at 156°C.

ALLYL PARA CHLORPHENYL THIO UREA and ACETYL CHLORIDE.

Allyl p-chlorphenyl thio urea and acetyl chloride in equivalent amounts were placed in a large test tube and heated slightly on the water bath. The oily mixture which

is produced by the reaction was dissolved in alcohol and made slightly alkaline with sodium carbonate solution. The 2-chlorphenyl amido, 5-methyl, 4,5-dihydro thiazole was precipitated as the free base and was purified from alcohol, mp. 116°C.

On analysis 0.2275 grams of the sample gave 16.75 cc of moist nitrogen at 25°C. and 740mm pressure.

Calculation as $C_{10}H_{11}N_2S\,Cl$

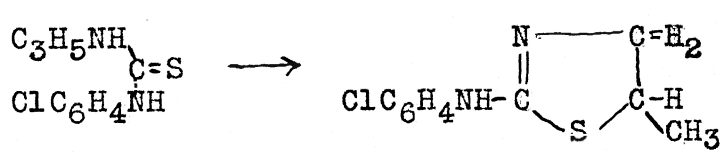
| Found | Theory |
|---|---|
| 12.58 | 12.40 |

The hydrochloride of the base was prepared by passing dry hydrogen chloride into the benzene solution of the substance. The salt melts at 226°C.

The hydrochloride was analyzed by titrating a known weight of it with a standard solution of sodium hydroxide.

Analysis as $C_{10}H_{12}N_2SCl_2$

| Found | Theory |
|---|---|
| 14.20 | 13.~~66~~ 14 % of hydrogen chloride. |

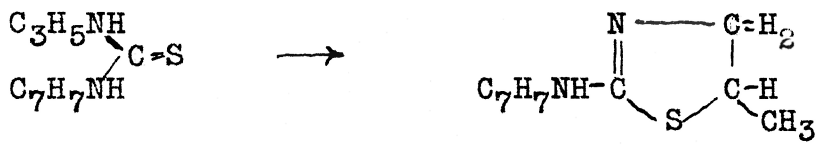


ALLYL PHENYL THIO UREA and ACETYL CHLORIDE.

Equivalent quantities of the urea and the acetyl chloride were heated on a water bath for thirty minutes. The product of the reaction was a thick oil which was dissolved

in alcohol and made slightly alkaline with sodium carbonate solution. The white precipitate, which was formed, was purified from alcohol. It melted at 116°C. and is the same product as that prepared from allyl phenyl thio urea and hydrochloric acid, p 25. This 2-anilido, 5-methyl, 4,5-dihydro thiazole is readily soluble in alcohol, gasoline and benzene and extremely so in chloroform.

ALLYL META TOLYL THIO UREA and ACETYL CHLORIDE.



In this reaction equal mols of the urea and acid chloride were placed in a large test tube and heated on the water bath for a short time. The reaction product is a light yellow liquid smelling strongly of acetyl chloride, which is converted into ethyl acetate by the addition of alcohol. The alcoholic solution was made slightly alkaline with sodium carbonate solution and a white precipitate was formed, which was 2-tolyl amido, 5-methyl, 4,5 dihydro thiazole. It was recrystallized from alcohol, mp. 90°C. This compound is readily soluble in alcohol, benzene, and gasoline and extremely so in chloroform . It is basic, dissolving readily in dilute acids and forms a picrate which melts at 158°C.

On analysis 0.2055 grams of the sample gave 25.25 cc

of moist nitrogen at 25°C. and 740 mm of mercury. Also 0.2290 grams of the substance gave 28.20 cc of moist nitrogen at 22°C. and 738 mm pressure.

Calculated as $C_{11}H_{14}N_2S$

| Found | Theory |
|---|---|
| 13.26 | 13.60 |
| 13.48 | |

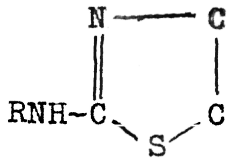
ALLYL PHENYL THIO UREA and BENZOYL CHLORIDE.

Equivalent quantities of the thio urea and benzoyl chloride were placed in a small flask and heated on a water bath for thirty minutes. The reaction product, a thick oil, was dissolved in alcohol and made alkaline with sodium carbonate. The impure solid, 2-anilido, 5-methyl, 4,5-dihydro thiazole, which was precipitated, was recrystallized from alcohol, mp. 115°C. This reaction involves the transformation of the allyl thio urea into the thiazole base whichhhas been shown in previous experiments to take place under the influence of hydrochloric acid or acetyl chloride. The products formed by the action of each of these acid reagents on allyl phenyl thio urea are identical.

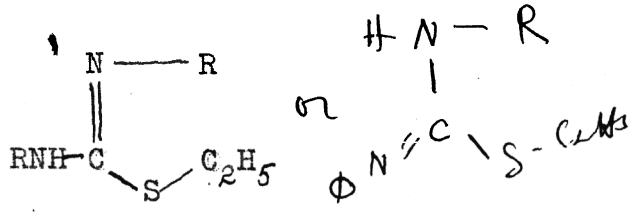
ANILIDO DI-HYDRO METHYL THIAZOLE and BENZOYL CHLORIDE with PYRIDINE.

In this thiazole we have a bonding similar to that of

the iso urea ethers.

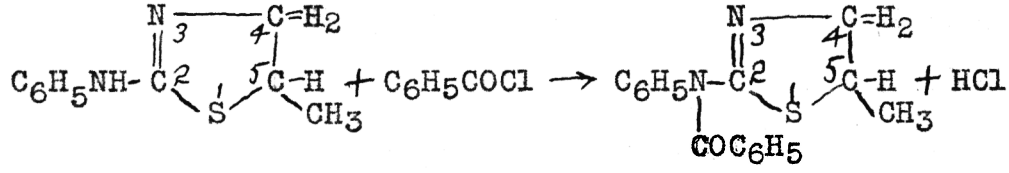


thiazole



isourea ether

The hydrogen atom of the anilido group of the isourea ether is replaceable by a benzoyl radical as has been shown by previous experiments. It would therefore seem that the the thiazole from analogy of bonding should react with benzoyl chloride, to form 2-benzoyl anilido, 5-methyl, 4,5-dihydro thiazole.



Of course there is a possibility that the benzoyl group is attached to the nitrogen atom at position three, instead of having the configuration given above.

The reaction was tried by dissolving ten grams of the thiazole in pyridine, and an equivalent amount of benzoyl chloride was slowly added with constant shaking. A considerable quantity of heat was evolved and a solid was precipitated which proved to be pyridine hydrochloride. It wa was filtered off and the pyridine solution allowed to stand over night. A crystalline product separated out and when purified from alcohol melted at 118°C. It is moderately

soluble in ether, readily soluble in carbon bisulphide, alcohol, benzene and gasoline, and extremely soluble in chloroform.

Although the melting point of this benzoyl derivative was nearly the same as that of the original thiazole, a mixture of equal parts of the twp products showed a depression of nearly thirty degrees in the melting point.

On analysis as $C_{17}H_{16}ON_2S$ by Kjeldahl method.

| Found | Theory |
|---|---|
| 9.65 | 9.46 % of nitrogen |
| 9.74 | |

The basic properties of the thiazole appear to have been destroyed by the addition of the acid radical. The benzoyl derivative did not form a picrate when a benzene solution of the substance was added to a benzene solution of picric acid. When the benzoyl derivative of the thiazole was boiled with alcoholic potash the original thiazole and benzoic acid were obtained, both of which were identified by their melting points.

Cold dilute hydrochloric acid will also bring about this hydrolysis showing that the benzoyl group is evidently held very loosely. It is interesting to compare the loose bonding of the benzoyl group in this compound with similar acyl derivatives of the isourea ethers which have been

described in previous experiments.

In conclusion I wish to express my appreciation to Dr. F. B. Dains for his many helpful suggestions during this work.

Chemical Laboratories,
University of Kansas.
May 12, 1915.